Respiratory Medicine (2007) **101**, 1609–1612

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respiratoryMEDICINE

CASE REPORT

Acute eosinophilic pneumonia caused by *Candida albicans*

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Received 25 January 2007; accepted 30 January 2007
Available online 26 March 2007

KEYWORDS
C. albicans;
Acute eosinophilic pneumonia;
IL-5;
Cell culture

Summary
A 36-year-old man was transferred to the hospital for further evaluation of pulmonary infiltration. A diagnosis of acute eosinophilic pneumonia (AEP) was confirmed by clinical symptoms, bronchoalveolar lavage, and computed tomography findings. Skin tests with fungal antigens were performed by intradermal injection. Both the Arthus (8 h) and delay (24 h)-type skin tests were positive for only *Candida albicans*. A lymphocyte-stimulating test was also positive for *C. albicans*. The etiology of the AEP was confirmed by a *C. albicans* inhalation provocation test. In addition, peripheral blood mononuclear cells obtained from the patient produced Interleukin-5 following *C. albicans* stimulation. This is the first report of *C. albicans* as a probable cause of AEP. Evaluation of allergy to *C. albicans* should be performed in AEP before diagnosing the cause as idiopathic.

Introduction

Acute eosinophilic pneumonia (AEP) was first described in 1989.[1,2] Since then, many factors such as drugs, cigarette smoke, and fungi have been implicated as causes of AEP.[3,4] There are few references in the literature regarding the role of *Candida albicans* in eosinophilic lung disease,[5] although it is well known that *C. albicans* is one of the aeroantigens that causes bronchial asthma and allergic bronchopulmonary candidiasis.[6] We present here the first case of acute onset eosinophilic pneumonia induced by *C. albicans*.

Case report

A 36-year-old man with cough, general fatigue, slight fever, and dyspnea was admitted to a local hospital. One week before admission, he complained of a cough. Thereafter,

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doi:10.1016/j.rmed.2007.01.024

general fatigue and dyspnea appeared. A chest radiograph on admission showed shadows disseminated over both the mid and lower lung zones. Chest computed tomography (CT) demonstrated diffuse ground glass opacities, reticular shadows, and alveolar septal thickening (Fig. 1). Bronchoalveolar lavage (BAL) was performed. The BAL count was 7.98×10^5/ml, with 65.5% eosinophils, 5.9% lymphocytes, 2% neutrophils, and 26.3% alveolar macrophages. The CD4:CD8 ratio in the bronchoalveolar lavage fluid (BALF) was 2.84. No pathogen was identified. The patient was diagnosed with AEP according to modified Allen's criteria.[1,7] His symptoms spontaneously improved without specific therapy.

One week after admission, he was transferred to our hospital for further evaluation of the disease. His past medical history revealed neither asthma nor any occupational exposure to toxic fumes, dust, or animals. He was a current smoker. Physical examination revealed a temperature of 36.8 °C and blood pressure of 119/49 mmHg. Lung auscultation revealed no abnormal sounds. There was no heart murmur. Arterial blood gases were as follows: pH 7.392, HCO_3 27.6 mmol/l, pCO_2 46.5 mmHg, pO_2 97.5 mmHg, and base excess 2.1 mmol/l. The white blood cell count (WBC) was $4.67 \times 10^3/mm^3$ with 6.7% eosinophils and 60.6% neutrophils. His hemoglobin concentration was 14.1 g/dl. C-reactive protein was 0.11 mg/dl. The total serum IgG, IgM, and IgA levels were 972 g/dl, 27 mg/dl (reference range [*R*]: 35–220), and 320 mg/dl, respectively, and total serum IgE was 348 IU/ml ([*R*]: <170). Specific IgE to 21 common aeroallergens, including fungi antigens, was negative. His chest radiograph was normal. A chest CT revealed that the alveolar septal thickening and the ground glass opacities had disappeared.

BAL was performed. Sterile saline (150 ml) was instilled into the right B8 segment in 50-ml aliquots. No pathogen was identified. The BAL count was 3.76×10^5/ml, with 13.4% eosinophils, 5.9% lymphocytes, 2% neutrophils, and 26.6% alveolar macrophages. The CD4:CD8 ratio in the BALF was 2.4. No organisms grew in the BAL culture.

Skin testing by intradermal injection revealed that both the Arthus (8 h) and delay (24 h)—type skin tests were positive for only *C. albicans allergens* (Torii Pharmaceutical; Tokyo, Japan), although the immediate reaction was negative. A lymphocyte-stimulating test (LST) for *C. albicans*, *Aspergillus fumigatus* (*A. fumigatus*), and *Alternaria alternata*, expressed as stimulatory index (SI) (over 180% is considered positive), yielded values of 290%, 199%, and 153%, respectively. We thought these clinical examinations were more consistent with allergy to *C. albicans*. A provocation test with *C. albicans* allergens (10,000-fold dilution) was performed with careful observation under informed consent. The patient developed a nonproductive cough 1 h after the provocation. Eighteen hours later, his body temperature had increased from 36.5 to 37.9 °C. The WBC count and C-reactive protein before the provocation were $5.70 \times 10^3/mm^3$ and 0.02 mg/dl, respectively, and rose to $23.0 \times 10^3/mm^3$ and 1.93 mg/dl after the provocation, respectively. PaO_2 deceased to 93.3 from 98.4 mmHg. Other than a cough and mild decease of PaO_2, radiologic changes did not appear after the provocation test.

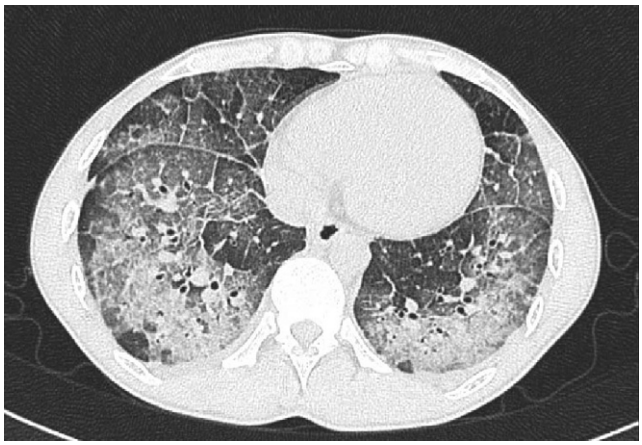

Figure 1 Chest CT demonstrated diffuse ground glass opacities, reticular shadows, and alveolar septal thickening.

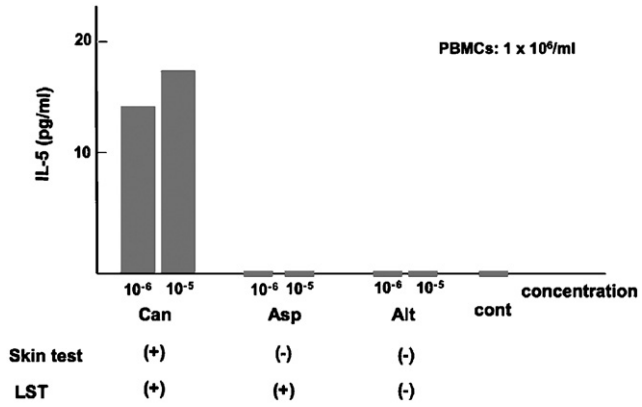

Figure 2 *C. albicans* allergens induced IL-5 production in an AEP patient. PBMCs obtained from our patient were cultured with various concentrations of fungal allergens for 3 days. IL-5 concentrations of the resulting supernatants were assayed by specific ELISA. LST: lymphocyte-stimulating test, Can: *C. albicans*, Asp: *A. fumigutus*, Alt: *Alternaria altrenata*.

To clarify the causal allergens for eosinophilic inflammation and exclude possibility of cross sensitization, peripheral blood mononuclear cells (PBMCs) obtained from the patient were stimulated with various fungal allergens and Interleukin-5 (IL-5) production was examined by enzyme-limked immunosorbent assay (Instant ELISA, Vender, Vienna). IL-5 production was only detectable in PBMCs stimulated with *C. albicans* allergens on day 3, although the proliferation response to *C. albicans* and *A. fumigatus* allergens (LST) was positive (Fig. 2). We therefore concluded that AEP was induced by *C. albicans*.

Discussion

AEP is characterized by a rapid onset of clinical symptoms and signs associated with the presence of diffuse pulmonary infiltrates on the chest radiograph and a high number of eosinophils in the alveoli.[1] AEP is most commonly idiopathic. Other conditions associated with eosinophils, however, can result in an AEP like clinical presentation. Thus, AEP can be viewed as a syndrome that is idiopathic or a result of several

causative conditions. Drug are sometimes associated with an AEP syndrome.[2] In addition, cigarette smoking was recently recognized to cause AEP (CS-induced AEP) in Japan, especially in a new-onset smoker.[8] Our patient, however, did not have drug-induced AEP and had a long smoking history.

Fungal hypersensitivity, especially to *Trichosporon terrestre* and *Aspergillus*, causes eosinophilic pneumonia.[9–11] Recently, *Alternaria altenata*, *Schizophyllum* commune, and *C. albicans* were reported to cause of chronic eosinophilic pneumonia.[12,13,5] To our knowledge, this case is the first reported case of AEP induced by *C. albicans*. A presumptive diagnosis of *C. albicans*-induced pneumonia was made on the basis of skin tests and LST results. The provocation test with *C. albicans* led to the diagnosis. A provocation test with specific antigens is useful for diagnosing pigeon breeder's disease,[14] hypersensitivity pneumonitis,[15] chronic eosinophilic pneumonia,[12] and smoking-induced AEP.[4,8] It might also be useful in determining the etiologic agents of eosinophilic pneumonia.

Shintani et al.[8] reported a case of CS-induced AEP showing tolerance. Other than cough and mild decrease of PaO_2, pulmonary symptoms of radiological change and blood eosinophilia did not appear after the provocation test in our case. Watanabe et al.[16] reported increase of eosinophils in both BALF and TBLB developed without significant radiological findings after challenge test. Neutrophilia in the lung or blood is usually found during the early phase of AEP.[17] Nakajima et al.[4] also reported that blood eosinophilia was not observed after cigarette-smoking challenge test.

An association between environmental fungal exposure and allergic pulmonary disease, such as asthma and interstitial pneumonia, has been recognized clinically. This association depends on immunologic reaction to endogenous allergen.[18,19] Mori et al.[20] reported that *C. albicans* was involved in eosinophil inflammation through the induction of IL-5 production by Th cell.

The relevance of this allergen was further supported by the induction of IL-5 production by patient's PBMCs. IL-5 has selective functions of eosinophil activation and recruitment and is produced by CD4-positive T cells. AEP is characterized by locally high levels of IL-5 in the alveolar space. There is evidence of increased production of IL-5 in the BALF of patients with AEP.[21] Taniguchi et al.[22] also reported that activated CD4 cells and IL-5 elevation contribute to the development of AEP. PBMCs obtained from our patients produced IL-5 upon stimulation with the *C. albicans* antigen, but not *A. fumigatus* or *Alternaria altrenata*, although the LST was also positive for *A. fumigatus*. These results indicated that *C. albicans* allergens have contributed to the airway eosinophilic inflammation through the induction of IL-5 production by T cells in the present case. Cellular immunity might therefore have an important role in pulmonary eosinophilia.

In conclusion, we report here the first known case of *C. albicans* induced-AEP. The clinical course, exclusion of alternative causes, skin test, detection of IL-5 production from PBMCs, and reaction to the provocation test were useful for determining the etiology of the AEP.

Conflict of interest. None.

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